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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/019,520	06/10/2002	Lakjaya Buluwela	20010529.ORI	8687

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EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 08/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/019,520	BULUWELA ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *53-106* is/are pending in the application.

4a) Of the above claim(s) *54,73,77 and 89-106* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *53,55-72,74-76 and 78-88* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4-02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Seq. Non-compliance notice*.

DETAILED ACTION

This Office action is in response to the communication filed 6-21-05.

Claims 53-106 are pending in the instant application.

Election/Restrictions

Applicant's election with traverse of Group I, claims 53, 55-72, 74-76 and 78-88, as they pertain to all or a portion of an androgen receptor DNA binding protein or polypeptide, and all or part of the PLZF chromatin inactivating protein or polypeptide, in the reply filed on 6-21-05 is acknowledged. The traversal is on the ground(s) that Groups I and II really are part of one generic invention. This is not found persuasive because, although the special technical feature of Groups I and II is considered to be a method of suppressing expression of eukaryotic genes comprising the administration of an entity that binds to a site on the eukaryotic genome and additionally comprising a chromatin inactivation entity, the two groups do not related to a single general inventive concept under PCT Rule 13.1 or 13.2. The polynucleotides of Group II, the polypeptides of Group I and the various inventions in either Group comprising different nucleic acid binding entities and chromosomal inactivation entities do not share common properties and common structures. No common structure unifies polynucleotides and polypeptides, or unifies nucleic acids encoding different nucleic acid binding entities and/or chromosomal inactivation entities. No common structure unifies polypeptides encoding different nucleic acid binding portions and/or chromosomal inactivation portions of different polypeptides. Furthermore, each

member of these different and distinct groups cannot be substituted one for the other with the expectation that the same intended result would be achieved.

The requirement is still deemed proper and is therefore made FINAL.

Claims 54, 73, 77 and 89-106 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 6-21-05.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 53, 55-72, 74-76 and 78-88 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is unclear in claim 53, lines 3-7, whether the "chromatin inactivation portion" disclosed in lines 6-7 is what the "nucleic acid binding portion" (line 4) also binds to, or is instead a separate part of the polypeptide disclosed in line 3. (Claim 53 is also objected to for the following reasons: "introduing" in line 3 is a misspelling; a comma should be inserted in line 2, before "the method".) Appropriate correction is required.

Claim 57 is not a grammatically correct sentence (*e.g.* inserting a comma after "wherein" in line 2 and inserting another comma after "protein" in line 4 would be remedial). Appropriate correction is requested.

In claim 81, line 2, it is unclear what is meant by "a plurality of selected gene". Appropriate clarification or correction is required.

Claims 82, 83 and 85 provide for the use of an agent for suppressing eukaryotic gene expression, but, since the claims do not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 82, 83 and 85 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 53, 55-72, 74-76 and 78-88 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are understood to be drawn to compositions and methods comprising administration of *a polypeptide which comprises a nucleic acid binding portion which binds to a site at or associated with a selected gene that is present in a eukaryotic genome*, which binding portion optionally comprises a *nuclear receptor DNA binding portion*, or wherein the DNA binding portion is selected from *a DNA binding part of a zinc finger DNA binding protein or all or a DNA binding part of helix turn helix DNA binding protein,* or optionally comprises *all or part of a steroid hormone receptor protein*; and which polypeptide further comprises a *chromatin inactivation portion*, which optionally comprises *an inactivation portion which comprises a portion of a component of a histone deacetylation complex (HDAC),* or *such portion that binds to or facilitates the recruitment of a HDAC.*

The disclosure and claims do not adequately describe the broad genera claimed (which genera are illustrated by italics above). The specification and claims do not describe the elements essential to each of the genera. The specification and claims do not indicate the distinguishing attributes concisely shared by the members of these broad genera - nor is there clarification of the common attributes encompassed by the *nucleic acid binding portions* claimed, or of the *chromatin inactivation portions* claimed. Thus, the scope of the claims includes numerous structural variants, and the genera are highly variant because a significant number of structural differences between members of each given genus is permitted. Concise structural features that could distinguish structures within a given genus from those outside of it are missing from the disclosure. No common structural attributes identify the members of the various genera. The

general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. The specification fails to teach or adequately describe a representative number of species in each genus such that common attributes or characteristics concisely identifying members of each proposed genus are exemplified. And because each genus is highly variant, the description provided is insufficient. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the various genera claimed. Thus, Applicant was not in possession of the very broad genera claimed.

Claims 53, 55-72, 74-76 and 78-88 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of suppressing the expression of an estrogen responsive reporter gene in breast cells in vitro comprising the administration of a nucleic acid construct encoding PLZF-ER-alpha (as described on p. 45 of the instant specification), and being enabling for a method of suppressing activation of an androgen responsive reporter gene in COS-1 cells in vitro comprising the administration of a nucleic acid encoding PLZF-AR, (as described on p. 49 of the instant specification) does not reasonably provide enablement for a method of suppressing the expression of any selected gene in any eukaryotic cell in vitro or in vivo comprising the administration of a polypeptide comprising any nucleic acid binding portion that binds to a site present in a eukaryotic genome and any chromatin inactivation portion. The specification does not enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to compositions and methods of suppressing the expression of any selected gene in any eukaryotic cell in vitro or in vivo comprising the administration of any polypeptide comprising any nucleic acid binding portion that binds to a site present in a eukaryotic genome and any chromatin inactivation portion.

The state of the prior art and the predictability or unpredictability of the art. The following references are cited herein to illustrate that the adequate delivery to a target cell in vivo of candidate polypeptides, for providing gene suppression or other treatment effects, is energy dependent and may require the presence of specific proteins that serve as receptors and/or channels in order to provide the needed polypeptide concentrations within the appropriate organelles in the target cells. Derossi et al teach the ability of antennapedia homeodomain to translocate through biological membranes, but this ability is highly sequence dependent, and illustrates that delivery of polypeptides to target cells is a rate limiting step for cell targeting and entry for most polypeptides (see D. Derossi et al. J. Biol. Chem. 269(14): 10,444-10,450, especially the abstract on p. 10,444, last paragraph of the introduction on p. 10,444; first full paragraph on p. 10,450: "Other polypeptides that cross biological membranes are those destined, after synthesis, to specific intracellular compartments such as the endoplasmic reticulum or the mitochondria... Passage through these intracellular membranes is energy-dependent and requires the presence of specific proteins that serve as receptors and/or channels. However, even in this rather well studied system,

the actual mechanism of importation is not yet completely understood." For specific requirements of other, specialized polypeptides involved in cellular membrane penetration, see M. Pooga et al. FASEB J. 12: 67-77 for a discussion of the remarkable properties of transportan; see also G. Elliott et al, Cell 88 : 223-233 for the distinguishing features of Herpes virus structural protein and its role in intercellular trafficking).

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. The specification teaches a method of suppressing activation of an androgen responsive reporter gene in COS-1 cells in vitro comprising the administration of a nucleic acid encoding PLZF-AR (which nucleic acid construct is described on p. 49 of the instant specification). The specification also teaches a method of suppressing the expression of an estrogen responsive reporter gene in breast cancer cells in vitro comprising the administration of a nucleic acid construct encoding PLZF-ER-alpha (which nucleic acid construct is described on p. 45 of the instant specification).

Applicants, however, have not provided adequate guidance in the specification for a method of suppressing gene expression in vitro or vivo comprising the administration of any polypeptide comprising any nucleic acid binding portion that binds to a site present in a eukaryotic genome and any chromatin inactivation portion. One skilled in the art would not accept on its face the examples given in the specification of the in vitro suppression of an estrogen responsive or androgen responsive reporter gene following the administration of the nucleic acid constructs specifically described in

the specification and comprising PLZF-AR or PLZF-ER-alpha as being correlative of the ability to deliver these or other polypeptides in appropriate concentrations to target cells in vitro or in vivo, whereby suppression of any eukaryotic is provided. There is a lack of guidance in the specification and an unpredictability associated with the successful targeting and delivery of polypeptides to target cells in vitro or in an organism, and further whereby the expression of any eukaryotic gene is suppressed.

The breadth of the claims and the quantity of experimentation required. The claims are broadly drawn to compositions and methods of suppressing the expression of any selected gene in any eukaryotic cell in vitro or in vivo comprising the administration of any polypeptide comprising any nucleic acid binding portion that binds to a site present in a eukaryotic genome and any chromatin inactivation portion. The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of formulations and methods of successfully delivering a representative number of polypeptides comprising any nucleic acid binding portion that binds to a site present in a eukaryotic genome and any chromatin inactivation portion whereby any gene is suppressed in an organism and in a target cell in vitro. Since the specification fails to provide sufficient guidance for the suppression of eukaryotic gene expression in any organism comprising administration of this broad genus of polypeptides, and since determination of the requisite factors is highly unpredictable, it would require undue experimentation to practice the invention over the broad scope claimed.

Related Prior Art

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Grignani, F. et al. (Nature, Vol. 391, pages 815-818, 1998) and Chien, P-Y, et al (Molecular Endocrinology, Vol. 13, No. 12, pages 1161-1167, 1993) teach methods of suppressing eukaryotic gene expression in vitro comprising the administration of nucleic acids encoding polypeptides comprising a DNA binding domain and a chromatin inactivation portion. They are distinguished from the elected claims because it would not be obvious why one would be motivated to administer polypeptides, rather than nucleic acids encoding polypeptides, to target cells, whereby the polypeptides must be delivered, in adequate concentrations and in proper conformation, to the nucleus for the suppression of gene expression.

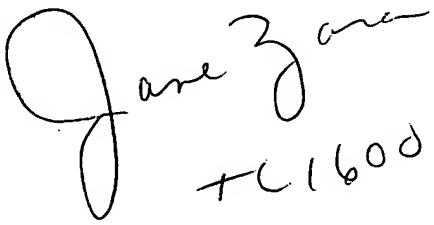
Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. ə 1.6(d)). The official fax telephone number for the Group is **703-872-9306**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, can be reached on (571) 272-0811. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jane Zara
8-2-05



Appl[illegible]ation No.:_____

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: Please provide Seq No's for Sequences in Figs & where otherwise Appropriate, in the Specification

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

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